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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/768,020	01/23/2001	Ralph J. Greenspan	P-NI 4577	9299

23601 7590 06/15/2004

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EXAMINER	
PRIEBE, SCOTT DAVID	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 06/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/768,020	GREENSPAN ET AL.	
	Examiner	Art Unit	
	Scott D. Priebe	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 April 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above claim(s) *1-21 and 30-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 March 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The Group and/or Art Unit designation of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Primary Examiner Scott D. Priebe, Ph.D., Group Art Unit 1632.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restrictions

This application contains claims 1-21 and 30-37 drawn to an invention nonelected with traverse in the reply filed on 8/12/02. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Drawings

The drawings filed 3/6/03 are objected to because the labeling of Figures 2-8 does not conform with 37 CFR 1.84(u)(1). For example the successive sheets making up Fig. 2 should be labeled Fig. 2A, 2B, 2C, etc. Corrected drawing sheets are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be

renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. The replacement sheet(s) should be labeled "Replacement Sheet" in the page header (as per 37 CFR 1.84(c)) so as not to obstruct any portion of the drawing figures. If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112

Claims 22-29 remain rejected under 35 U.S.C. 112, first paragraph, for the reasons of record set forth in the Office action of 10/6/03, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant's arguments filed 4/6/04 have been fully considered but they are not fully persuasive. Applicant asserts that page 14 and Tables 4-6 of the specification disclose several dozens of examples of Alzheimer's disease genes. In response, the specification (page 14, lines 13-17) defines an "Alzheimer's disease gene" as meaning "a homolog of a human gene that has genetic variants associated with an increased risk of Alzheimer's disease or that encodes a gene product associated with Alzheimer's disease". The specification then asserts that the *Drosophila* genes listed in lines 23-30 of page 14 are "Alzheimer's disease genes". However, there is no evidence of record that the homologous human genes of any of these *Drosophila* genes, or the

products of the human homologs, have been implicated in Alzheimer's disease, so there is some question that these genes satisfy the definition set forth in the specification.

Also, these *Drosophila* genes were identified as being genes that when a genetic variation in the gene, e.g. a deletion, was introduced into a fly with at least one $Appl^D$ gene, the resulting double heterozygote (test progeny) had a different phenotype that a single heterozygote (sibling control). The claims require a pair of parent strains that when mated produce the required test progeny. One parent strain must carry the mutation in an Alzheimer's disease gene, e.g. a fruit fly with at least one $Appl^D$ gene. If one were to choose a parent strain with a mutation in a different Alzheimer's disease gene, e.g. *Presenelin*, the specification fails to disclose a parent strain with a "genetic variation", that when crossed into a fly having a mutant *Presenelin*, would produce the required test progeny. For example, the specification discloses (page 61, lines 3-7) that double heterozygotes for mutations in the Appl and Presenelin genes did not have an altered viability phenotype relative to sibling controls.

In addition, the genes listed on page 14 are *Drosophila* genes, and most of the claims are not limited to *Drosophila* parent strains. The specification fails to identify appropriate parent strains of other organisms.

Claims 22-29 remain rejected under 35 U.S.C. 112, first paragraph, for the reasons of record set forth in the Office action of 10/6/03, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant's arguments filed 4/6/04 have been fully considered but they are not fully persuasive. Applicant asserts that the specification teaches a variety of behavioral, morphological, and physical phenotypes that may be used to practice the invention with several different organisms. Applicant points out that the specification identifies chromosomal deficiencies that in combination with *Appl*^{D} decrease or increase "viability" (i.e. produce fewer or more double-heterozygous progeny than expected from a simple two-factor cross; viability of adult test progeny was not assessed) or result in changes to fast phototaxis behavior. (Applicant refers to teachings on page 24 of the specification in the first paragraph of page 8. However, page 24 is part of Table 2.) Applicant points out that the disclosures of Luo et al. and Fossgreen et al. support a structural and functional homology between Appl in *Drosophila* and mammalian App.

In response, the issue is not whether different genotypes of organisms have been known to result in different phenotypes, but what parent strains of a particular organism should be used and what phenotypes are observed among test progeny of a mating between the recited first and second parents that differs from the sibling controls, and how such a phenotype would relate to Alzheimer's disease in humans. The specification does not identify suitable combinations of parent strains for organisms other than *Drosophila*. With *Drosophila*, the specification identifies parent strains having a "genetic variation," which are mostly loss of function mutations, that when mated with male flies that are hemizygous for *Appl*^{D} produce fewer or more double-heterozygous progeny than expected from a simple two-factor cross, indicating that the genes in which the "genetic variation" occurs interact at some level with the Appl gene. However, the

specification fails to disclose how reduced function of the Appl gene alone or in combination with an interacting loss-of-function genetic variation relates to Alzheimer's disease in humans.

Alzheimer's disease is characterized by insoluble deposition of the β-amyloid peptide of the human App protein, which is observed to occur at higher levels in humans carrying certain App alleles. While Luo and Fossgreen support the hypothesis that Appl and App are functionally similar and have common ancestral origin, the function of App and Appl is not known and there is no evidence of record that the function of App itself, whether normal or aberrant, is involved in Alzheimer's disease. Luo discloses that the *Drosophila* Appl protein has homology to the human App protein over much of the protein, but not in the region of the β-amyloid peptide in App. Thus, the *Drosophila* Appl protein does not have the feature of the human App protein that is critical for Alzheimer's disease. Fossgreen discloses that expression of full-length human App in *Drosophila* results in an aberrant phenotype that is independent of β-amyloid peptide production. Also, expression of full-length human App in *Drosophila* does not result in production or deposition of the β-amyloid peptide.

In addition, $Appl^{D}$ is a loss of function mutation that results in a reduction of Appl protein levels in the flies. Alzheimer's disease is thought to result, at least in part, from the deposition of the β-amyloid peptide in neurons due to aberrant processing of the App protein, i.e. the presence of the protein is necessary.

Thus, there appears to be no logical or scientific basis for proposing that an agent that affects the altered phenotype of the $Appl^{D}$/genetic variant double heterozygotes disclosed in the specification would have any effect on Alzheimer's disease in humans.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott D. Priebe whose telephone number is (571) 272-0733. The examiner can normally be reached on M-F, 8:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy J. Nelson can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Scott D. Priebe

Scott D. Priebe
Primary Examiner
Art Unit 1632